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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/686,317	10/15/2003	Susan M. Freier	IBIS0009-101 (ISPH-0794)	8250
34138	7590	02/21/2008	EXAMINER	
ISIS PHARMACEUTICALS, INC 1896 RUTHERFORD ROAD CARLBAD, CA 92008			VIVLEMORE, TRACY ANN	
			ART UNIT	PAPER NUMBER
			1635	
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No. 10/686,317	Applicant(s) FREIER ET AL.	
	Examiner TRACY VIVLEMORE	Art Unit 1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 26 November 2007.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 17 and 40-42 is/are pending in the application.
- 4a) Of the above claim(s) _____ is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 17 and 40-42 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
 2. ☐ Certified copies of the priority documents have been received in Application No. _____.
 3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- | | |
|--|---|
| 1) <input checked="" type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input type="checkbox"/> Interview Summary (PTO-413) |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | Paper No(s)/Mail Date. _____ |
| 3) <input type="checkbox"/> Information Disclosure Statement(s) (PTO/SB/08) | 5) <input type="checkbox"/> Notice of Informal Patent Application |
| Paper No(s)/Mail Date _____ | 6) <input type="checkbox"/> Other: _____ |

DETAILED ACTION

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Any rejection or objection not reiterated in this Action is withdrawn.

Claim Objections

Claim 17 is objected to because of the following informalities: at each occurrence of the word "motif" it appears this should be in the plural, not the singular. Also, at line 11, the word "sequence" should also be in the plural. Appropriate correction is required.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

Claims 17 and 40-42 are rejected under 35 U.S.C. 103(a) as being unpatentable over Smetsers et al. (of record) in view of Torrence et al. (US 6,214,805) and Bennett et al. (of record).

The claims are directed to methods of selecting antisense-sequences by providing a set of antisense sequences complementary to a target nucleic acid sequence, eliminating from the set sequences comprising 5'-GGGG-3' and 5'-GGA-3',

selecting sequences comprising 5'-CCAC-3'; and synthesizing antisense oligonucleotides having the selected sequence. In specific embodiments the synthesized oligonucleotides are chimeric, have at least one 2'-substituted nucleotide and are tested *in vitro* for their ability to modulate the target nucleic acid.

Smetsers et al. teach that antisense oligonucleotides have been used successfully in a number of biologic models in an attempt to modulate gene expression, but that several publications show that in some cases the antisense effect is not caused by-an antisense-mediated inhibition of translation of mRNA. A number of specific motifs of two, three or four nucleotides responsible for non-sequence-specific effects have been identified. Smetsers et al. analyzed the composition of effective antisense oligonucleotides to investigate if particular nucleotide sequence motifs are preferentially used and to get an impression of the importance of certain sequence stretches in the effects induced by oligonucleotides. Smetsers et al. teach that the motif 5'-TCC-3' is underrepresented in the antisense oligonucleotides analyzed, indicating that the presence of this motif may negatively affect antisense activity. The complement of the 5'-TCC-3' motif is 5'-GGA-3' and due to the rules of complementarity of nucleotides, one of ordinary skill would expect that if a motif binding to its complementary sequence has a physical characteristic that negatively affects antisense activity, the same effect should occur when the complementary sequence is present in the antisense strand. Smetsers et al. do not teach that 5'-GGGG-3' is a motif absent from active antisense oligonucleotides.

It was well known to those of ordinary skill in the art at the time the invention was made that the presence of four contiguous G residues in a nucleotide sequence will induce a non-specific inhibitory effect due to formation of a G-quadruplex structure. Knowledge of this concept is demonstrated by the teachings of Torrence et al., who describe at column 26 that a sequence complementary to sequences occurring within the critical gene-end-intragenic-gene-start signals of RSV genomic RNA exhibited antiviral effect. However, it was noted that this antisense sequence contained a G₄ motif. A control oligonucleotide scrambled so as to not match the target sequence but also containing a G quartet motif was found to also have significant antiviral activity. Torrence et al. conclude that a significant non-antisense effect would be inherent in any oligonucleotide targeted to this 17-mer consensus sequence due to the presence of the G-quartet.

Bennett et al. disclose antisense oligonucleotides targeted to human protein kinase C, several of which have 5'-CCAC-3' motifs and lack 5'-GGGG-3' or 5'-GGA-3' motifs (see, for example, SEQ ID NOs: 1, 34, 57, 67, 79 and 81). At columns 7-8 Bennett et al. disclose that the oligonucleotides may contain 2'-substitutions or be synthesized as chimeras. In the working examples Bennett et al. disclose the synthesis and *in vitro* testing of these sequences for their ability to inhibit human protein kinase C.

It would have been obvious to one of ordinary skill in the art at the time the invention was made to produce antisense oligonucleotides that do not contain motifs that would be expected to decrease activity such as 5'-GGA-3' and 5'-GGGG-3' as taught by Smetsers et al. and Torrence et al. One of ordinary skill in the art would also

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find it obvious to test oligonucleotides for their activity and would recognize that once oligonucleotides containing 5'-GGA-3' and 5'-GGGG-3' are removed, the selection for testing of oligonucleotides having a 5'-CCAC-3' motif is a matter of design choice, exemplified by Bennett et al., who teach the synthesis and testing of several oligonucleotides that contain 5'-CCAC-3' motifs and lack 5'-GGA-3' and 5'-GGGG-3' motifs.

Thus, the invention of claims 17 and 40-42 would have been obvious, as whole, at the time the invention was made.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Tracy Vivlemore whose telephone number is 571-272-2914. The examiner can normally be reached on Mon-Fri 8:30-5:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, J. Douglas Schultz, can be reached on 571-272-0763. The central FAX Number is 571-273-8300.

Patent applicants with problems or questions regarding electronic images that can be viewed in the Patent Application Information Retrieval system (PAIR) can now contact the USPTO's Patent Electronic Business Center (Patent EBC) for assistance. Representatives are available to answer your questions daily from 6 am to midnight (EST). The toll free number is (866) 217-9197. When calling please have your application serial or patent number, the type of document you are having an image

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For all other customer support, please call the USPTO Call Center (UCC) at 800-786-9199.

/Tracy Vivlemore/
Examiner
Art Unit 1635

TV
February 15, 2008